ANTI-OX40 BINDING PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a National Stage Application of International Application No. PCT/US2017/045788, filed Aug. 7, 2017, which claims priority to U.S. Provisional Application No. 62/371,993, filed on Aug. 8, 2016, and entitled "Anti-OX40 Binding Proteins", the entire contents of each of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Feb. 7, 2019, is named Sequence_Listing_S103014_2040US.PCT.txt and is 100 kilobytes in size.

BACKGROUND

OX40 (also known as CD 134, TNFRSF4, ACT35 or TXGP1L) is a member of the TNF receptor superfamily, which includes 4-1BB, CD27, CD30 and CD40. The extracellular ligand binding domain of OX40 is composed of 3 full cysteine-rich domains (CRDs) and a partial, fourth C-terminal CRD (Bodmer et al, 2002, *Trends Biochem. Sci.*, 27, 19-26). The ligand for OX40, OX40L, is a member of the TNF family and is expressed on activated antigen presenting cells (APC), including B cells, macrophages, endothelial cells and dendritic cells (DC). OX40 is a membrane-bound receptor; however a soluble isoform has also been detected (Taylor and Schwarz, 2001, *J. Immunol. Methods,* 255, 67-72). OX40 is not expressed on resting T cells, but is transiently expressed on activated T cells after ligation of the T cell receptor (TCR).

OX40 is a major costimulatory receptor with sequential engagement of CD28 and OX40 resulting in optimal T cell proliferation and survival. Ligation of OX40 on activated T cells leads to enhanced cytokine production and proliferation of both CD4+ and CD8+ T cells (Gramaglia et al., 2000, *J. Immunol,* 165, 3043-3050, Bansal-Pakala et al., 2004, *J. Immunol.,* 172, 4821-425) and can contribute to both ongoing Th1 and Th2 responses (Gramaglia et al., 1998, *J. Immunol.,* 161, 6510-6517, Arestides et al, 2002, *Eur. J. Immunol.* 32, 2874-2880). OX40 costimulation prolongs T cell survival beyond the initial effector phase of the immune response and increases the number of memory T cells through inhibition of effector T cell death.

When immune activation is excessive or uncontrolled, pathological allergy, asthma, inflammation, autoimmune and other related diseases may occur.

Tumor cells commonly 'escape' the immune system by induction of an active immune tolerance largely mediated by regulatory T lymphocytes (Tregs et al. *Immunol Rev.* 2011; 241:104-118). Therefore, the balance between effector (i.e., direct or indirect eradication of tumor cells) T lymphocytes (Teffs) and tolerogenic (i.e., suppression of Teffs effector function and survival) Tregs appears to be important for effective anti-tumor immunotherapy. In other words, an effective anti-tumor immune response can be obtained by enhancing effector function of tumor-specific Teffs and/or by attenuating suppressive function of tumor-specific Tregs. A key receptor that has been shown to mediate these responses is OX40 (CD134). (Sugamura et al., *Nature Rev. Imm.* 2004; 4: 420-431).

In vivo ligation of mouse CD134 receptor (by either soluble mouse OX40 ligand (OX40L)-immunoglobulin fusion proteins or mouse OX40L mimetics, such as anti-mouse CD134-specific antibodies) in tumor-bearing mice enhances anti-tumor immunity, leads to tumor-free survival in mouse models of various murine malignant tumor cell lines, e.g., lymphoma, melanoma, sarcoma, colon cancer, breast cancer, and glioma (Sugamura et al. *Nature Rev. Imm.* 2004; 4:420631). Al-Shamkhani et al. (*Eur. J. Chem.* 1996; 26: 1695-1699) used an anti-OX40 antibody called OX86, which did not block OX40L-binding, in order to explore differential expression of OX40 on activated mouse T-cells; and Hirschhorn-Cymerman et al. (*J. Exp. Med.* 2009; 206: 1103-1116) used OX86 together with cyclophosphamide in a mouse model as a potential chemoimmunotherapy.

Thus, there remains a need in the art for effective treatments based on OX40, particularly anti-OX40 antibodies.

SUMMARY OF THE INVENTION

The invention provides antibodies that specifically bind to OX40, including human OX40.

In a first aspect, the invention features an isolated anti-OX40 antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain comprising a heavy chain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID Nos: 49, 50 and 51; SEQ ID Nos: 55, 56 and 57; SEQ ID Nos: 61, 62 and 63; SEQ ID Nos: 67, 68 and 69; SEQ ID Nos: 73, 74 and 75; SEQ ID Nos: 79, 80 and 81; SEQ ID Nos: 85, 86 and 87; SEQ ID Nos: 91, 92 and 93; SEQ ID Nos: 103, 104 and 105; SEQ ID Nos: 109, 110 and 111; SEQ ID Nos: 118, 119 and 120; SEQ ID Nos: 133, 134 and 135; SEQ ID Nos: 139, 140 and 141; SEQ ID Nos: 148, 149, and 150; SEQ ID Nos: 157, 158 and 159; SEQ ID Nos: 163, 164 and 165; SEQ ID Nos: 172, 173 and 174; SEQ ID Nos: 178, 179 and 180; SEQ ID Nos: 184, 185 and 186; SEQ ID Nos. 195, 196 and 197; and SEQ ID Nos. 203, 204 and 205; and a light chain variable domain comprising a light chain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID Nos: 52, 53 and 54; SEQ ID Nos: 58, 59 and 60; SEQ ID Nos: 64, 65 and 66; SEQ ID Nos: 70, 71 and 72; SEQ ID Nos: 76, 77 and 78; SEQ ID Nos: 82, 83 and 84; SEQ ID Nos: 88, 89 and 90; SEQ ID Nos: 94, 95 and 96; SEQ ID Nos: 97, 98 and 99; SEQ ID Nos: 100, 101 and 102; SEQ ID Nos: 106, 107 and 108; SEQ ID Nos: 112, 113 and 114; SEQ ID Nos: 115, 116 and 117; SEQ ID Nos: 121, 122 and 123; SEQ ID Nos: 124, 125 and 126; SEQ ID Nos: 127, 128 and 129; SEQ ID Nos: 130, 131 and 132; SEQ ID Nos: 136, 137 and 138; SEQ ID Nos: 142, 143 and 144; SEQ ID Nos: 145, 146 and 147; SEQ ID Nos: 151, 152 and 153; SEQ ID Nos: 154, 155 and 156; SEQ ID Nos: 160, 161 and 162; SEQ ID Nos: 166, 167 and 168; SEQ ID Nos: 169, 170 and 171; SEQ ID Nos: 175, 176 and 177; SEQ ID Nos: 181, 182 and 183; SEQ ID Nos: 187, 188 and 189; SEQ ID Nos: 190, 191 and 192; SEQ ID Nos. 198, 199 and 200; SEQ ID Nos. 206, 207 and 208; SEQ ID Nos. 210, 211 and 212; and SEQ ID Nos. 214, 215 and 216. In one embodiment, the heavy chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 24, SEQ ID NO. 29, SEQ ID NO. 31,